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REMARKS

In the previous Office Action, the Examiner acknowledged Applicant's election of species, and withdrew claims 5 and 6 from further consideration. Claims 1-4 and 7 are under examination in the instant application. Claims 1, 2 and 4 have been amended to address the Examiner's concerns under 35 U.S.C. §112, second paragraph. In particular, claim 1 has been amended to specify that the spinal canal is the *central* canal; claim 2 has been modified to include the steps of withdrawing a volume of blood from the patient; and obtaining the growth or differentiation factors from the volume of blood; and claim 4 has been amended to specifically recite BMP-1 as a growth factor (in dependent form). With regard to the objection to claim 3, it is Applicant's position that such techniques are described in enabling detail in Applicant's disclosure. In the alternative, such methods are well known to those of skill in the art. Recombinant growth techniques and extraction methods are well known in the art, and need not be recited in detail.

Pending claims 1-3 and 7 stand rejected under 35 U.S.C. §112 (first paragraph) as being non-enabling. Regarding claims 1-3, the Examiner cites In re Wands, 8 U.S.P.Q.2d, 1400 (CAFC 1988), which sets forth factors which may be considered in determining whether a disclosure would require undue experimentation. As the court concludes, whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.

The Examiner remarks that spinal injections are "usually given" into the relatively large space above the spinal cord and dura (Office Action, page 6), demonstrating some familiarity with these techniques. Spinal injections, and methods of performing them, are well known to those skilled in the medical arts. I t is not necessary for Applicant to describe in detail what is already well known to those skilled in the medical arts. A patent need not disclose what is well known in the art. In re Wands.

APPLICANT'S PENDING CLAMS ARE ENABLED UNDER 35 USC §112, FIRST PARAGRAPH

The Examiner argues that the breadth of the claims embraces many types of growth factors. Claim breadth is a factor cited in In re Wands as tending against patentability. However, after

restriction, the claims are currently drawn to the use of bone morphogenic proteins. Hence, in this case, the claim specificity tends towards patentability. In re Wands.

Several researchers have studied the effects of BMP on articular chondrocytes. BMP-2 has been shown to induce chondrocytes differentiation, to maintain chondrocyte phenotype in cell culture, stimulate proteoglycans synthesis by chondrocytes, and enhance the expression of type II collagen. Submitted herewith is a report by Yoon et al. from the Journal *Spine* (Vol. 28, No. 16 pp 1773-1780). According to this article, 2003, Yoon et al. were the first researchers to test the effects of rhBMP-2 on disc cells. The article shows BMP-2 has a positive effect on disc cells; in particular, BMP stimulates disc cell reproduction, proteoglycans synthesis by disc cells, and type II collagen synthesis by disc cells. BMP also help preserve the phenotype of the cultured disc cells. This research proves that rhBMP-2 has a positive effect on disc cells and articular chondrocytes.

APPLICANT'S CLAIMS COVER BONE MORPHOGENIC PROTEINS IN GENERAL

Although the Yoon et al. article focuses on BMP-2, there are practical reasons for this, including convenience and availability for research. Given the abundant supply of rhBMP-2, many studies have been performed with rhBMP-2. Nevertheless, all BMP molecules are very similar in structure and function. As noted by A. Hari Reddi in his chapter "Bone Morphogenetic Proteins and Related Cytokines" in the text TGF-Beta and Related Cytokines in Inflammation, S.N. Breit & S.M. Wahl (editors) Birkhauser Verlag, Basel 2001, p. 150, "BMPs are dimeric molecules and the conformation is critical for biologic actions. Reduction of the single intermolecule disulfide bond resulted in the loss of biological activity.

"The mature monomer of BMPs consists of about 120 amino acids, with seven canonical cysteine residues. The cysteine knot is the critical central core of the BMP molecule." In other words, although the structures of all TGF-Beta molecules are similar, the molecular structure of BMP proteins is more highly conserved. Consequently, proteins with this very similar structure are placed into the BMP sub-group of the TGF-Beta family of cytokines.

Cytokines are proteins that regulate wound healing, wound repair, regulation of inflammation, cell growth, cell reproduction, and cell differentiation. The TGF-Beta superfamily is a specific family of proteins within the broad group of cytokines. Members of the TGF-Beta family

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share a similar structure. The dimeric TGF-Beta molecules have a highly conserved pattern and spacing of cysteine residues. Bone Morphogenetic Proteins are one of seven sub-families within the TGF-Beta superfamily of cytokines.

All the BMPs induce chemotaxis, mitogenesis, and differentiation of cells. All BMPs induce the cascade of chondrogenesis. BMPs are the only growth factors that are capable of inducing new bone formation. BMPs, as a family, also bind to specific matrix molecules. In fact, BMP molecules are so similar that BMPs from mammals are active in flies, and BMPs from flies can induce cartilage and bone formation in mammals.

Twenty different types of BMPs have been discovered. Many of the more recently discovered BMPs have not been expressed as recombinant proteins. Thus, researchers have limited quantities of these newly discovered BMPs to work with. Despite the limited supply of some types of BMPs, several of the BMPs have been tested on chondrocytes and fibrocytes. The cells of the nucleus pulposus (NP) of the intervertebral disc are similar to chondrocytes. Fibrocytes are found in the annulus fibrosus (AF) of the disc. Encouraged by the effects of BMPs on cartilage, researchers have just started to test the effects of BMPs on the cells of the disc. Most of the research on BMPs has focused on BMP-2, BMP-7, and BMP-14. Recombinant techniques have yielded a large supply of the three types of BMP.

Although all types of BMPs have not been tested on the cells of the disc, research to date suggests that BMPs that have a positive effect on chondrocytes will likely have similar positive effects on disc cells. BMPs 3, 4, 6, 7, 12, 13, and 14 have been tested on articular chondrocytes. The studies suggest that these BMPs preserve chondrocyte phenotype in cell culture, promote cartilage matrix synthesis, and promote chondrogenesis. BMPs 12, 13, & 14 have been shown to promote neotendon/ligament formation. As noted above, the AF is rich in fibrocytes and is tendon like.

As the other types of BMP become more readily available they will be tested on chondrocytes and disc cells. Given the highly conserved shape of BMP proteins those of skill can presume the BMPs that have not been tested on chondrocytes and disc cells will likely have similar positive effects on chondrocytes and disc cells as seen with the BMPs listed above. For example, given the large supply of rhBMP-7, many studies have demonstrated the positive effects rhBMP-7 has on chondrocytes. BMPs 5 and 6 are more similar in structure to BMP-7 than BMP-2 is similar

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to BMP-7. Yet, BMP-2 has been shown to have the similar positive effects on chondrocytes as BMP-7.

In summary, the finding of Yoon et al. is that BMP-2 is likely beneficial to disc cells. Studies testing the effects of BMPs 7 and 14, both now available in large supply, are optimistic in terms of their effect on chondrocytes, which would suggest that they will benefit disc cells. The studies of Yoon et al., though subsequent to Applicant's filing date, point to clear enablement by one of skill in the relevant art. The other research regarding the similarities and effects of BMP-n prove that Applicant is entitled to coverage at least with respect to this broad class of biological materials.

Respectfully submitted,

By: _____

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